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Maureen Gorsen, Director
Department of Toxic Substances Control
California Environmental Protection Agency
1001 I Street
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Dear Dr. Gorsen:

The following recommendations are submitted on behalf of the tens of thousands of California members of the Physicians Committee for Responsible Medicine and People for the Ethical Treatment of Animals. As California residents ourselves we appreciate the opportunity to contribute and look forward to continued involvement in California's Green Chemistry (GC) initiative.

We are concerned that GC recommendations may include calls for large amounts of toxicity testing involving animals, and have prepared some comments and recommendations to address this concern. The timely and thorough evaluation of potential chemical hazards requires intelligent strategies for prioritization and evaluation, and we urge the California EPA to employ this approach when drafting its GC initiative recommendations.

California cares about animals in laboratories

Scientific experts representing animal protection groups such as PCRM and PETA work on a national and international level to push for the reduction and replacement of animals in laboratory testing, while ensuring the protection of the environment and human health. As awareness of the scientific and ethical problems with standard animal-based toxicity testing grows, our expertise is increasingly sought by the EPA and other federal agencies, the Organisation for Economic Co-operation and Development (OECD), the US's Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM), the European Centre for the Validation of Alternative Methods (ECVAM), the European Commission, and within the chemical and toxicity testing industry. These organizations recognize that because we focus specifically on animal protection in context of regulatory assessment, our scientists are experienced at devising creative solutions that would circumvent the use of animals in laboratory testing. The contributing members of PCRM and PETA, nearly 75,000 of these living in California, entirely support efforts to reduce the use of animals in laboratories, as evidenced by the large number of posted recommendations generated by an e-mail to our California members,.

Problems with animal-based toxicity tests

One post on the Cal/EPA on-line Forum suggests that it is necessary to characterize the specificity and sensitivity of *in silico* and *in vitro* tests before their use and we are in agreement. A scientific evaluation of any new safety test is of course appropriate and necessary. However, one must also keep in mind that the sensitivities and specificities of currently-employed animal-based toxicity tests have never been fully investigated or taken into account in any consequential way. While *in vitro* methods must be scientifically validated, there is no such requirement for *in vivo* tests to show reproducibility or relevance. For example, ECVAM estimated in a 2005 study that based on historical data for 171 rabbits that the rabbit pyrogen test had a sensitivity of 57.9% and a specificity of 88.3%.[1] The 2-year rodent cancer bioassay is under increased scrutiny;[2] a comprehensive review of all 502 the National Toxicology Program 2-year cancer bioassays conducted, and published reports, determined that results are reproducible only 57% of the time.[3] An examination of teratology test data for 11 groups of known human teratogens across 12 animal species reveals a mean sensitivity of 61%[4]. The developmental neurotoxicity test—a test that uses thousands of animals each time it is conducted—is a relatively new protocol currently in use that has still not been validated according to the principles of the OECD's own Guidance Document on validation.[5]

These examples illustrate a concept that regulators and others have recognized for years but have failed to communicate or act upon: statistically, animal-based toxicity assessments do not predict outcomes in humans. It is only recently that regulatory authorities have begun to face this problem—California must not fall back onto reliance on these methods as it is aiming to lead us into the future in chemicals policy.

Barriers to the use of non-animal methods

A workshop convened in 2005 by the International Society of Regulatory Toxicology and Pharmacology (ISRTP) and attended by a broad base of scientists and policy experts from industry, regulatory agencies, and animal protection groups identified major barriers to the acceptance and use of non-animal toxicity testing methods to be institutional. Inadequate funding and resources, as well as "regulator comfort," topped the list.[6] This

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[1] Hoffmann S, Peterbauer A, Schindler S, et al (2005). International validation of novel pyrogen tests based on human monocytoid cells. *J Immunol Methods* 298: 161-173.

[2] F.K. Ennever, L.B. Lave / Regulatory Toxicology and Pharmacology 38 (2003) 52–57

[3]Wasted Money, Wasted Lives: A Layperson's Guide to the Problems With Rodent Cancer Studies and the National Toxicology Program. People for the Ethical Treatment of Animals. Available at: http://www.stopanimaltests.com/pdfs/Wasted$$$.pdf.

[4] Bailey J, Knight A, and Balcombe J (2005). The future of teratology research is in vitro. *Biogenic Amines* 19(2):97–145.

[5] Guidance Document Number 34: Guidance Document on the Validation and International Acceptance of New or. Updated Test Methods for Hazard Assessment. OECD 2005.

[6] Becker R, Borgert C, Webb S, et al (2006). Report of an ISRTP Workshop: Progress and barriers to incorporating alternative toxicological methods in the U.S. *Regulatory Toxicology and Pharmacology* 46:18–22.

sentiment was echoed this year in a report by the Committee on Toxicity Testing and Assessment of Environmental Agents, convened by the National Academy of Sciences, at the request of the EPA, to draft a vision of the future of toxicity testing: "[C]urrent toxicity-testing practices are long established and deeply ingrained in some sectors. Thus, some resistance to the vision proposed by this committee is expected."[7]

International consensus among scientists and policymakers regarding ICCVAM, the entity charged with validating and promoting non-animal toxicity tests, is that progress has not kept pace with technology. Inadequate funding and personnel, lack of a focused vision, and inadequate leadership has led to the dismal record of three validated methods in ten years, one of which only partially replaces an animal test and two of which still use live animals. This can be compared with ECVAM's progress, with over 20 methods accepted and more than 150 undergoing development.

In the event that Cal/EPA recommends or develops testing policies or procedures, guidance must include measures that insure the development and incorporation of relevant, reliable and predictive non-animal methods, and must not be limited to ICCVAM-validated methods.

Lessons from other initiatives

Throughout the GC initiative process, a number of chemical regulation programs have been reviewed in terms of how California should (and should not) proceed. These programs also have positive and negative characteristics from an animal protection standpoint. For example, a number of EPA scientists view work on prioritization and evaluation of new chemicals under TSCA, using QSAR and other tools they have developed, as a successful venture. The Canadian EPA can be applauded for its prioritization scheme. It took a realistic approach to chemicals information gathering and management by using simple tools to "bin" chemicals based on what it already knew and focusing on those of highest concern. For chemicals without any data, data from analogous chemicals, genetic toxicology, physicochemical properties, and QSAR tools were used to consider the chemicals' priority ratings.

Animal protection scientists had extensive involvement in the EPA's High Production Volume Chemical Challenge Program (HPV), starting with a push for basic animal welfare considerations which were then transmitted to chemical producers and suppliers.[8] We worked to suggest alternatives to proposed tests, often finding that manufacturers proposed duplicative tests due to incomplete data searches and missed opportunities for bridging data among similar chemicals. Additional animal testing was conducted when companies did not know about, or declined to apply, basic animal welfare principles. Other companies made stellar efforts to reduce animal testing by using the initial EPA

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[7] The National Academy of Sciences Committee on Toxicity Testing and Assessment of Environmental Agents (2007). Toxicity testing in the 21st century: A vision and strategy. National Academy of Sciences, Washington, DC.

[8] Wayland SH (1999). Letter to manufacturers/importers. Available at: http://www.epa.gov/chemrtk/ceoltr2.htm

strategies as well as strategies developed by animal protection scientists. These strategies were later used as a basis for further recommendations in the E-HPV program, a continuation of the original HPV program. Another, cautionary lesson of this program is that voluntary programs, while allowing for increased flexibility, make it difficult to enforce animal protection measures.

Although the European REACH legislation is held by some as a model for chemical evaluation programs, problems with implementation have yet to be discovered. Initial upper estimates regarding the number of animals killed while existing chemicals undergo the registration process neared 40 million. Fortunately, tireless lobbying by European animal protection groups and others has instituted policies that will reduce this number, such as *in silico* screening models, tiered testing, weight-of-evidence, category and read-across strategies, and the use of "scientifically appropriate" non-animal alternatives tests as they are developed and deemed so by ECVAM. The absence of appreciable exposures or production volumes can waive some toxicity testing in some cases. Additionally, the use of so-called "alternative" data, such as data generated under non-Good Laboratory Practice conditions and historical human data are allowed. These measures represent an important positive step in the incorporation of animal protection measures into the REACH chemicals program. However it remains to be seen whether these measures will be followed once the program is put into practice.

In determining how chemical prioritization and evaluation will fit into the GC initiative, California must evaluate the positive and negative aspects of all past, existing, and future programs, and should determine how best to incorporate these aspects into its policies without duplicating them.

All of these programs, as well as others not mentioned here, have generated toxicity data. It is of urgent and extreme importance that California negotiates access to this and other data, whether publicly available or not, to avoid duplicative testing. As experience has shown in the HPV program, chemicals companies cannot be relied upon to avoid duplicative testing. In many cases, it is easier and less expensive for them to simply check a box that requires animal testing than to comb through files of existing data or develop a thoughtful weight-of-evidence approach.

Recommendations

Based on the information above and to ensure appropriate chemical evaluation as part of a larger GC initiative, we make the following recommendations:

- Conduct a detailed, comprehensive assessment of existing laws, regulations and programs and ensure that recommendations for chemical screening, prioritization and evaluation include lessons learned from those programs. Cooperative agreements with existing programs are essential to avoid duplicative or ineffective efforts.

- Conduct a detailed, comprehensive assessment of existing chemical toxicity reporting and data availability programs and ensure access to those data as applicable to California. Assurances of some measure of formulation confidentiality would encourage producers and manufacturers to make toxicity and use data available.

- Information on chemical importation, use, and exposure patterns in California should be quantified and analyzed before requiring the generation of toxicity data; exposure and use data can and should be used to prioritize chemicals.

- A static, required list of toxicity tests should be avoided as check-the-box toxicology; instead, tiered, thoughtful testing strategies should be pursued with flexibility and creativity. For example, bioaccumulation, biopersistence, solubility, and other physicochemical parameters should be determined prior to conducting dose-related evaluations such as percutaneous absorption testing; moving up from there would involve a full characterization of the chemical or material using in vitro cell and tissue assays. For the sake of flexibility as science advances a list of required tests promulgated legislatively should be avoided.

- Ensure committees, meetings, and programs are publicly open at multiple stages. While the initial process for this initiative is public, and there were many opportunities for public comment and discussion, it is unfortunate that there will not be an opportunity for the public to react to the initial DTSC recommendations before they are transmitted to the Secretary for Environmental Protection for finalization.

- Seek input from animal protection stakeholders, who have a unique set of qualifications and can specifically address the reduction and replacement of *in vivo* animal tests, before recommending testing strategies or regulations.

- The National Academy of Science's recent report addressing the future of toxicity testing[9] should be embraced as part of a GC initiative, not only in the interest of animal welfare, but in the interest of a healthy environment. Issues of emerging concern, such as the toxicity of mixtures and synergistic effects, nanotechnology, low-dose effects, and the timing of exposures in the life cycle, as well endocrine, immunological, and neurological effects, combined with the sheer number of existing and new chemicals, require a new way of evaluating chemicals. The vision of the NAS report, which calls for a reinvention of toxicity testing using high-throughput *in vitro* and *in silico* screens and tests based on human relevance, should be backed wholeheartedly by California. One tool that deserves special mention as a way to move this vision forward is the ToxCast program, in its first phase at EPA. The EPA is looking to enter into cooperative agreements with other entities in order to complete future phases. Additional information can be found

[9] The National Academy of Sciences Committee on Toxicity Testing and Assessment of Environmental Agents (2007). Toxicity testing in the 21st century: A vision and strategy. National Academy of Sciences, Washington, DC.

on the Web: http://www.epa.gov/osp/ftta.htm. Funding, resources, ideas, and other contributions are necessary in order to help this vision come to fruition, and it is both within the capabilities of California and required by the vision of GC to do so.

- Other projects to promote more intelligent and/or human-based toxicity evaluation schemes are currently being pursued and should be incorporated into GC policy recommendations. These include: The OECD QSAR Toolbox and other International QSAR Foundation activities, OECD and NTP toxicogenomics initiatives, ILSI/HESI's Tiered Toxicology Testing Proposal for Pesticide Chemicals, the OECD Integrated Approaches to Testing and Assessment workshop (taking place in December of 2007), as well as others such as those presented during the Cal/EPA workshop October 1-2, 2007. We also encourage coordination with the FDA and pharmaceutical manufacturers.

- Despite the necessity of creating new human-relevant toxicity testing strategies, there are barriers to this goal as discussed above. As part of the GC initiative, California should put incentives into place for chemical manufacturers and testing laboratories to develop and validate human-relevant methods. These can include grant awards, tax incentives, or forms of product stewardship recognition.

Thank you for your attention to these comments. We look forward to continued participation in the development of a Green Chemicals policy for California, and can be reached at the contact information below with any questions.

Sincerely,

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